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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/436,184	11/08/99	WANDS J	04930/032001

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EXAMINER	
CANELLA,K	
ART UNIT	**PAPER NUMBER**
1642	16

DATE MAILED: 01/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/436,184	Wands et al
Examiner	**Group Art Unit**
Karen Canella	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3 months* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-38* is/are pending in the applicat

Of the above, claim(s) *1-9 and 16-38* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *10-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of Group II, claims 10-15, in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-38 are pending. Claims 1-9 and 16-38, drawn to non-elected inventions, are withdrawn from consideration. Claims 10-15 are examined on the merits.

Claim Rejections - 35 USC § 112

3. Claims 10-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting growth of a mammalian tumor cell in culture or a method for inhibiting a mammalian tumor cell line grown in culture, said methods comprising the administration of a HAAH antisense nucleic acid consisting of the full length antisense HAAH cDNA as well as antisense DNA corresponding to exon 1 of the HAAH gene, does not reasonably provide enablement for a method for inhibiting tumor growth in a mammal comprising the administration of a HAAH antisense nucleic acid, ribozyme or intrabody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(A)As drawn to a method of inhibiting tumor growth in a mammal.

An effective therapeutic protocol for the treatment or prevention of the formation of a tumor is subject to a number of factors which enter the picture beyond simply the inhibition of expression of a single enzyme, such as aspartyl beta hydroxylase. Demonstrating the inhibiton of aspartyl beta hydroxylase expression in tumor cells cannot alone support the predictability of the method for prevention of or treating said tumor growth through administration of either an antisense nucleic acid or an intrabody directed to aspartyl beta hydroxylase. Tumor growth is a complex and multiple step process that proceeds by the aquistion of successive genetic insults (A.

Hagemeijer, Leukemia, 1992, Vol. 6, Suppl. 4, pp. 16-18). The establishment and growth of a tumor is subject to variables beyond the overexpression of a single enzyme. The ability of a host to suppress and thereby prevent the tumor from establishing itself will vary depending upon factors such as the condition of the host, the type and stage of tumor and the tumor burden.
(B)As drawn to the administration of an antisense nucleic acid in vivo.

Claims 11 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of an antisense nucleic acid. Claim 15 further embodies the inhibition of a CNS tumor. The specification does not enable the scope of the claims, drawn to inhibition of tumor growth in a mammal for the reasons put forth in paragraph (A) supra. The specification teaches the use of the full length antisense HAAH cDNA as well as antisense DNA corresponding to exon 1 of the HAAH gene were used to decrease the level of expression of the HAAH polypeptide in hepatocyte carcinoma cells, and alter the morphology of the treated cells to resemble a more differentiated phenotype. The specification does not teach the decreased level of expression of the HAAH polypeptide or the alteration of cellular morphology in a tumor in situ. The specification does not teach the decreased level of expression of the HAAH polypeptide, or alterations in cell morphology in any CNS tissue, in vitro or in vivo.

It is recognized in the art that the development of clinically useful antisense strategies for disease therapy is fraught with difficulties, even when the nucleic acid sequence for the target protein is known. Antisense nucleic acids, such as antisense cDNA or antisense exons, that are large and highly charged often interact with a wide variety of untargeted cellular components causing undesirable "non-antisense effects" (A.Branch, Hepatology, 1996, Vol. 24, pp. 1517-1529). Antisense nucleic acids must be optimized for use in patients. Additionally, it is well know in the art that the use of modified anti-sense oligonucleotides on CNS targets are limited by the powerful ability of the blood-brain barrier to exclude such anti-sense oligonucleotide. In order to use anti-sense technology for treatment of CNS pathologies, careful consideration must be made with respect to the target nucleotide sequence within the gene of interest, the choice of backbone modifications for the oligonucleotide, and the presence of special sequence motifs which predispose the oligonucleotide to undesirable non-antisense effects (Broaddus et al,

Methods in Enzymology, 2000, Vol. 314, pp. 121-135). The published data indicates that only a small percentage of the antisense oligonucleotides which are tested in vitro are actually effective in the reduction of the target mRNA, and that the ability of the anti-sense oligonucleotides to bind to a target mRNA cannot be predicted due to the structure and conformation assumed by individual mRNA specie (Broaddus et al, pg. 122). Further, even if the specific structure and conformation of a particular mRNA could be adequately predicted as an isolated molecule in a protein-free environment, it would not anticipate the accessible sites for the anti-sense oligonucleotide in vivo, wherein proteins are available to bind to the mRNA thus obscuring the oligonucleotide binding sites and potentially altering the conformation of the target mRNA. Broaddus et al teaches that a highly empirical approach to the testing of candidate anti-sense oligonucleotides is critical for the establishment of an antisense oligonucleotide as a therapeutic agent for the treatment of patients. This requirement has not been met by the instant specification, therefore, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

(C)As drawn to the administration of a ribozyme.

Claim 12 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of a ribozyme which inhibits the expression of the HAAH polypeptide. The specification does not enable the scope of the claim, drawn to inhibition of tumor growth in a mammal for the reasons put forth in paragraph (A) supra. Further, the specification does not discuss or demonstrate ribozyme cleavage sites within the nucleic acid sequence of the HAAH gene or the accessibility of the HAAH mRNA cleavage site to a ribozyme (S. Sullivan, 1994, Journal of Investigative Dermatology, Vol. 103, No. 5, Suppl., pp. 85S-89S). Messenger RNA is subject to secondary and tertiary sequence interactions resulting in a complex three dimensional structure which cannot be adequately predicted. Further, the synthetic ribozyme must be taken up by the tumor tissue, and it is well know in the art that uptake of a synthetic ribozyme into a cell is low (Sullivan, p. 87S, Ribozyme Delivery). Clearly the specification has not enabled the design of a ribozyme which would efficiently catalyze the mRNA from the HAAH gene, nor has the specification given instruction for the dose regiment to be used, nor the mode of delivery in vivo,

in order to effectively target the claimed tumor cells. One of skill in the art would be forced into undue experimentation to make and use the claimed invention.

(D)As drawn to the administration of intrabodies.

Claim 10 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of a compound which inhibits the expression of the HAAH polypeptide. The specification does not enable the scope of the claim, drawn to inhibition of tumor growth in a mammal for the reasons put forth in paragraph (A) supra. The specification teaches a number of monoclonal antibodies which are useful for binding to an epitope of the HAAH polypeptide which is exposed on the surface of the cell (pg 2, lines 25-29). The specification briefly discusses the basic principles of an intrabody (pg 2-3, lines 30-4). However, the specification does not disclose a specific intrabody, by amino acid sequence or by means of a biological deposit, that would act to efficiently bind the HAAH polypeptide endogenously and thereby inhibit the growth of a tumor in vivo. In order to produce intrabodies the nucleic acid sequences, of minimally the complimentary determining region, are necessary (Jones et al., Advanced Drug Delivery Reviews 1998, page 154, column 1, lines 18-26, and page 160, lines 24-25). The specification clearly fails to describe the nucleic acid sequences of an entire intrabody let alone the necessary complimentary determining regions. An intrabody by definition is an antibody that is expressed inside of a cell as a therapeutic agent. In order to get expression of an intrabody, especially in cells of the central nervous system an efficient means of transferring the genes is necessary. Clearly, the specification fails to describe the necessary delivery vehicles for the insertion and expression of an intrabody in a CNS tumor or any other tumor in situ.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

5. Claims 10, 11, 13 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Radosevich (USP 6,166,176). Claims 10, 11, 13 and 14 are drawn to the inhibition of tumor growth comprising the administration of the HAAH antisense nucleic acid. Further embodiments include tumors derived from endodermal tissue and liver cancer. Radosevich discloses that the protein coding region of the labyrinthin gene comprises the protein coding region of the HAAH gene (column 7, lines 7-11). Radosevich discloses the use of the full-length antisense labyrinthin cDNA to reduce the growth rate of A549 cells (column 9, second paragraph), which are tumor cells derived from a hepatocellular carcinoma.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
January 14, 2001

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